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Distichiasis-Lymphedema Syndrome: Tetralogy of Fallot, Chylothorax, and Neonatal Death

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We describe a newborn female with a severe presentation of distichiasis-lymphedema syndrome (McKusick 15340). She was initially evaluated because of a phenotype suggestive of Ullrich-Turner or Noonan syndrome (low posterior hairline, cupped ears, severe pterygium colli, heart murmur, and pectus excavatum). Distichiasis was noted at age 6 weeks. Subsequent to surgery for tetralogy of Fallot, patent ductus arteriosus, and branch pulmonic stenosis, she developed persistent chylothorax and sepsis. She died at 3 months. Family history indicated segregation of distichiasis-lymphedema syndrome. She was the sixth member in her family to have this disorder and was the most severely affected. © 1996 Wiley-Liss, Inc.

KEY WORDS: distichiasis, lymphedema, chylothorax, congenital heart disease, tetralogy of Fallot, pterygium colli

INTRODUCTION

Goldstein et al. [1985] previously described a mother and her four children with the distichiasis-lymphedema syndrome, congenital heart disease, and mild peripheral vascular anomalies. We report a new first degree relative in the third generation of that family with a severe presentation and we extend the phenotype of this disorder.

CLINICAL REPORT

This female infant was delivered by a 32-year-old G_1 mother whose prenatal history was complicated at about 34 weeks by pregnancy-induced hypertension and diet-controlled gestational diabetes. Fetal ultrasound studies at 20 and 24 weeks showed renal pelvic dilation and at 37 weeks hydronephrosis and a breech presentation at 37 weeks. Version was performed successfully at 38 weeks. The infant was delivered vaginally at 39 weeks. Apgar scores were 5 and 8 at 1 and 5 minutes, respectively. Weight was 3,185 g (50th centile), length was 48 cm (10th centile), and OFC was 33.5 cm (40th centile). At birth she was noted to have a sloping forehead, a low posterior hairline, normal eye measurements, posteriorly angulated and cupped ears that measured 3.3 cm (50th centile), laterally "built-up nose", high-arched palate, micrognathia, evident nuchal edema (Fig. 1), mild pectus excavatum, and a heart murmur. Internipple distance was 9 cm (75th centile). External genitalia were normal. Skin was mottled. Limbs were normal with no edema. Toenails were small.

At age 2 hours she became dusky. Echocardiogram showed tetralogy of Fallot, branch pulmonic stenosis, a small main pulmonary artery and left pulmonary artery, and a patent ductus arteriosus. Results of renal ultrasound study and angiography were normal. She also had normal vertebrae on radiographs, a normal hearing test, and normal ophthalmologic findings at age 1 week.

The patient underwent repair of her tetralogy of Fallot and ligation of the patent ductus arteriosus at age 2 weeks. Shortly thereafter, she developed pleural effusions and bilateral chylothorax, which initially were exacerbated by feeding. Mediastinal exploration with oversewing of leaking lymphatic vessels and sclerosis of pleural spaces was performed at age 1 month because of persistent chylothorax. Hypoplasia of the lymphatics was noted at surgery. Distichiasis was noted for the first time at the age of 6 weeks. She continued to have chylothorax and underwent repeat thoracotomy at which time the lymphatic vessels around the esophagus and descending aorta were clipped, the thoracic duct was ligated, and chemical pleurodesis was induced with doxycycline. She went on to develop a thrombus at the superior vena cava-right atrial junction and required heparin thrombolysis. She required amphotericin therapy for the subsequent development of candida sepsis. She died of idiopathic septic shock and renal failure at age 3 months. She also had gangrene of

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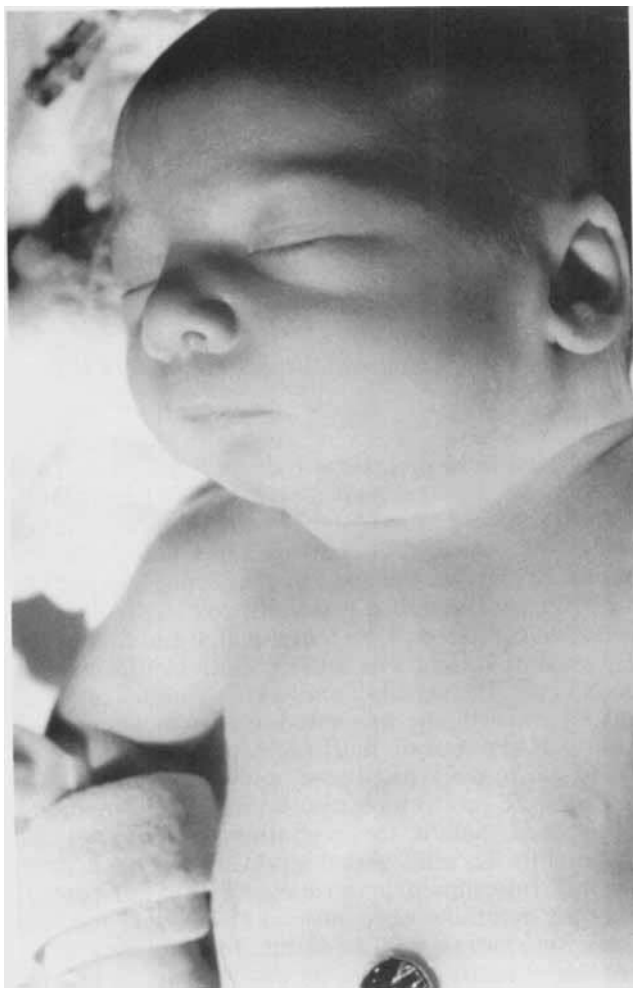

Fig. 1. Proposita shortly after birth; note nuchal folds, and micrognathia, but no distichiasis.

the fingers due to peripheral hypoperfusion at the time of her demise.

DISCUSSION

Genetic consultation was initially requested because of the phenotypic suggestion of Ullrich-Turner or Noonan syndromes. Ullrich-Turner syndrome was ruled out by a normal karyotype, 46, XX. A presumptive diagnosis of distichiasis-lymphedema syndrome was initially made in this patient, despite the initial apparent absence of distichiasis, based on the family history and inference from a review of the literature. Distichiasis-lymphedema syndrome is present in the patient's mother, three of the mother's sibs, and the maternal grandmother as previously described [Goldstein et al., 1985]. The updated pedigree is illustrated in Figure 2.

Distichiasis-lymphedema syndrome has been confused with Ullrich-Turner syndrome in two teenagers [Toro-Sola, 1991], but there are no case reports of similar confusion in newborn infants. With respect to similarities between Noonan syndrome and distichiasis-lymphedema, lymphatic dysplasia is reported in less than 20% of patients with Noonan syndrome, and spontaneous chylothorax can be a rare complication in Noonan syndrome secondary to hypoplasia of the lymphatic vessels resulting in obstruction, lymphangiectasis, and retrograde flow of lymph into the tissues [Goens et al., 1992].

Generally, post-operative chylothorax is unilateral and self-limiting. In this patient it was bilateral, persistent, and life-threatening. These findings plus the fact that the right pleural space was never entered during any of the surgical procedures and that the lymphatic channels were noted to be hypoplastic in the first surgery strongly suggest that congenital lymphatic dysplasia with or without absence or malformation of the thoracic-duct was the underlying cause of the persistent chylothoraces. To the best of our knowledge this is the first reported instance of bilateral, chylous pleural effusion in association with the distichiasis-lymphedema syndrome. This contrasts sharply with the commonly reported instances of bilateral lymphedema in the lower limbs, which usually appears during adolescence [Kolin et al., 1991; Schwartz et al., 1979; Robinow et al., 1970].

It is also important to recognize that distichiasis may not be present at birth in the distichiasis-lymphedema syndrome. Because of the family history this patient was carefully examined for the presence of distichiasis at age 2 days by several physicians, including an ophthalmologist, and it was not present. It did not appear until the 6th week of life.

The family history has several interesting components which may or may not be generalized or associated with distichiasis-lymphedema syndrome. Thus far, it appears that in this particular family, only the females have congenital heart disease. The maternal grandmother has a small ventricular septal defect and both the mother and maternal aunt had patent ductii arterioses requiring surgery, and this patient had tetralogy of Fallot. The maternal grandmother has diabetes mellitus type II (diet-controlled), the maternal aunt presumably has diabetes type II (diet-controlled) but required insulin during a pregnancy and this patient's mother had gestational diabetes. Two maternal uncles have ichthyosis of the limbs. The maternal grandmother has idiopathic proteinuria and wears hearing aids, and a maternal uncle has calcium oxalate kidney stones, an abnormal intravenous pyelogram showing sponge kidneys, and a high frequency hearing loss.

In summary we present a patient with an atypical variety of the distichiasis-lymphedema syndrome who extends the phenotype into a severe range with lethal outcome in infancy and demonstrates that there can be considerable phenotypic variability between members of a family afflicted with this disorder. Additionally, this is the first reported case of distichiasis-lymphedema syndrome to have had associated persistent, bilateral chylous pleural effusions presumably due to underlying congenital lymphatic dysplasia with absence or malformation of

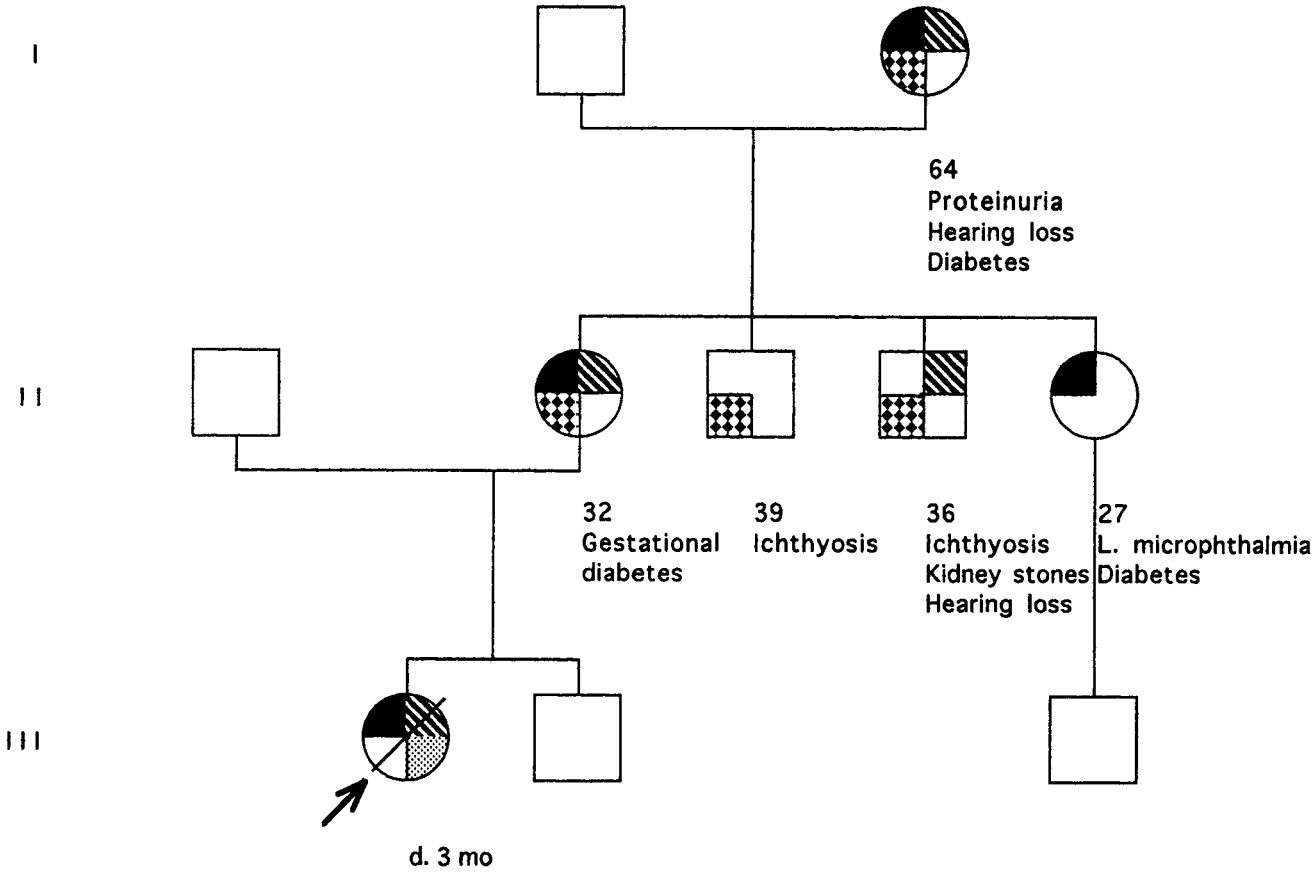

Fig. 2. Pedigree updating Goldstein et al. [1985] and showing proposita of the present study. Right upper quarter, lymphedema; left upper, heart defect; left lower, vertebral anomalies; right lower, chylothorax.

the thoracic duct. Finally, this patient documents delayed appearance of the second row of eyelashes until the 6th week of life.

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